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Original paper

Relative biological effectiveness study of Lipiodol based on microdosimetric-kinetic model☆

Daisuke Kawahara[a,b,*], Hisashi Nakano[c], Shuichi Ozawa[d,e], Akito Saito[d], Tomoki Kimura[d], Tatsuhiko Suzuki[b], Masato Tsuneda[b], Sodai Tanaka[f], Yoshimi Ohno[a], Yuji Murakami[d], Yasushi Nagata[d,e]

[a] Radiation Therapy Section, Department of Clinical Support, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima City, Hiroshima 734-8551, Japan
[b] Medical and Dental Sciences Course, Graduate School of Biomedical & Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima City, Hiroshima 734-8551, Japan
[c] Hiroshima Heiwa Clinic, State of the Art Treatment Center, 1-31 Kawara-machi, Naka-ku, Hiroshima City, Hiroshima 730-0856, Japan
[d] Department of Radiation Oncology, Institute of Biomedical & Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima City, Hiroshima 734-8551, Japan
[e] Hiroshima High-Precision Radiotherapy Cancer Center, 10-52 Motomachi, Naka-ku, Hiroshima City, Hiroshima 730-8511, Japan
[f] Department of Nuclear Engineering and Management, School of Engineering, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

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ABSTRACT

Objectives: We examine the contrast agent Lipiodol effect on the relative biological effectiveness (RBE) values for flattening filter free (FFF) and flattening filter (FF) beams of 6 MV-Xray (6 MVX) and 10 MVX.
Methods: Lipiodol was placed at 5 cm depth in water. According to the microdosimetric kinetic model, the RBE values for killing the human liver hepatocellular cells were calculated from dose and lineal energy ($yd(y)$) from Monte Carlo simulations. RBE_{200kVX} and RBE_{Co} were defined as the ratios of dose using reference radiation (200 kVX, Co-ϒ) to the dose of test radiation (FFF and FF beams for 6 MV and 10 MV) to produce the same biological effects. The dose enhancement RBE (RBE_{DE}) was defined as the ratios of a dose without Lipiodol to with Lipiodol using to produce the same biological effects. The dose needed to achieve 10% ($D_{10\%}$) and 1% cell survival ($D_{1\%}$) was evaluated by cell surviving fraction (SF) formula.
Results: The deviation of mean $\bar{y}_D$ values with and without Lipiodol were 3.9–4.8% for 6 MVX and 3.5–3.6% for 10 MVX. The RBE_{200kVX} and RBE_{Co} with Lipiodol were larger than that without Lipiodol. The RBE_{DE} was larger for FFF beam than for FF beam. The deviation of RBE_{DE} for FFF and FF beams of 6 MVX was larger than that of 10 MVX.
Conclusion: The presence of Lipiodol seemed to locally increase the absorbed dose and to also cause an enhancement of the relative biological effectiveness.

1. Introduction

There have been studies about the dose enhancement in the target using gold nanoparticles (AuNPs) [1–3]. The dose enhancement by AuNPs were analysed using various Monte Carlo (MC) simulations [4–6]. Tsiamas et al. reported spectral clinical beams around AuNPs with high spatial resolution and a dose enhancement factor (DEF) ranging from 1 to 100 depending on the energy of the photon beam and the type of study [7]. Our previous study reported the effect of dose distribution in Lipiodol (Guerbet, Villepinte, France) irradiated by a 10 MVX flattening filter free (FFF) beam [8]. Lipiodol has been used as an embolic agent and for tumour seeking in *trans*-arterial chemoembolization (TACE). Lipiodol that includes a high-atomic number material, such as iodine, has remained in tumour region on radiation therapy and it caused the dose enhancement. A Varian TrueBeam linear accelerator (linac) has a flattening filter (FF) and FFF beam. The removal of the flattening filter largely decreases the beam attenuation and it also affects the photon energy distribution, knowing that the FFF beam includes a large number of low-energy photons by comparing with FF beam [9]. Thus, the dose enhancement between FF and FFF beams could be different.

Although we reported the large dose enhancement in Lipiodol [8],

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* Corresponding author at: Radiation Therapy Section, Department of Clinical Support, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima City, Hiroshima 734-8551, Japan.
E-mail address: daika99@hiroshima-u.ac.jp (D. Kawahara).

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the biological effect was not shown. DEF values cannot be directly translated to the relative biological effectiveness (RBE). The RBE accounts for the dosimetric enhancement itself but also for all biophysical and biochemical processes induced by the ionising radiation leading to lethal or sub-lethal, irreparable or repairable damages and the subsequent death or survival of cells. Therefore, it is likely that there is a nonlinear relation between the RBE and DEF. Although RBE equal to 1.1 is currently assumed for proton radiation therapy, the RBE is defined as unity for megavoltage X-ray and electrons in general [10]. However, Joiner, et al. reported that damage to the tissue or cells with photon irradiation depends on the photon energy and dose rate [11]. The investigated photon energies were changed owing to the treatment machine and the phantom. The RBE variation with photon energy was experimentally observed in the previous studies [12–15]. Okamoto et al. reported the RBE for the killing of human salivary gland (HSG) tumour cells irradiated with 200 kV X-rays (200 kVX) and 6 MV X-rays (6 MVX) [16]. Not all types of model can help to provide better understanding of the mechanisms relating the physical dose and the RBE but a model relating both could still be useful, e.g. clinically. Although, there are some different models for predicting the RBE, the linear–quadratic (LQ) model is widely used. In the LQ model, the surviving fraction (SF) is given by:

$$S = e^{(-\alpha D-\beta D^2)}, \quad (1)$$

where S is the survival fraction, and α and β are parameters depending on the cell lines and dose rates as well as the profiles of radiation in a complicated manner. In many cases, the LQ curve fits fairly well to the survival data. However, in the past study, Brenner et al. reported that the β value depends on the dose-rate time structure [17,18]. Other past study reported an increasing β with increasing LET [19,20]. Thus, the LET is still controversial because of the experimental uncertainty associated with the available data and the difficulties characterizing its measurement. Microdosimetric-kinetic (MK) model that can predict the β value with increasing LET was created as a new model [21,22]. Moreover, this model takes into account the spatial distribution of the energy deposition of radiation. In this model, the survival fraction can be expressed as a function of dose-mean lineal energy, $\bar{y}_D$, by statistical derivation on the assumption that the variation of the energy is deposited in a subunit [23,24].

In this study, we simulate the cell survival and calculate the RBE using an MK model that is estimated based on the β value in the LQ formula for Lipiodol using human liver hepatocellular cells (HepG2). In addition, the correlation between the RBE and the dose enhancement and the RBE difference between the FF and FFF beams were investigated.

2. Methods and materials

2.1. Dose calculation with MC

Geant4, and EGSnrc codes are the most widely used computational tool in medical physics [25]. An important special-purpose code built on the EGSnrc platform is the user code BEAMnrc [26]. This code is optimized to model the treatment head of radiotherapy linacs, and includes several geometry and source subroutines, together with variance reduction techniques to enhance the efficiency of the simulation [27]. PHITS can deal with the transport of nearly all particles, including neutrons, protons, heavy ions, photons, and electrons, over wide energy ranges using several nuclear reaction models and nuclear data libraries [28]. In the present study, dose distribution using a TrueBeam linac (Varian Medical Systems, Palo Alto, USA) for FFF and FF beams of 6 MVX and 10 MVX was analysed. The components of the TrueBeam accelerator's head are proprietary and not available to the public for direct simulations. However, Varian provides IAEA-compliant phase-space files that were simulated using the GEANT4 MC code, located just above the secondary X/Y collimator. The phase space was scored onto the surface of a cylinder located above the secondary collimator. Therefore, the phase-space files below the secondary collimator were modelled using BEAMnrc. The phase-space data scored at a source-to-surface distance (SSD) of 90 cm. These phase-space files are used as a source in the PHITS calculation. The virtual phantom was created, and then dose calculation and biological effect were calculated using PHITS. The dose-calculation grid size was 2.0 mm. The cut-off energies for photons and electrons were set to 0.01 MeV and 0.7 MeV, respectively. The number of photon histories in BEAMnrc and PHITS were 2.0×10^8 and 2.0×10^9, respectively. The MC calculations were validated by comparing the simulation results with the results of the measurements. The percent depth dose (PDD) was measured using a 0.04 cm^3–volume CC04 (IBA Dosimetry, TN, USA) chamber, for a 10×10 cm^2 field, at an SSD of 100 cm.

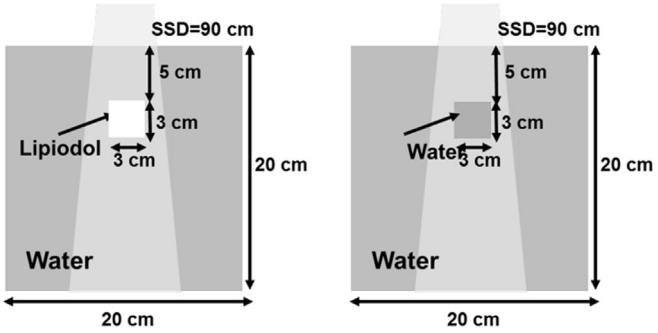

Fig. 1. Geometric scheme of Lipiodol located at a depth of 5.0 cm in a water-equivalent phantom ($20 \times 20 \times 20$ cm^3).

A virtual inhomogeneity phantom was used to calculate the dose enhancement in Lipiodol in the MC simulation, with Lipiodol ($3 \times 3 \times 3$ cm^3) located at a depth of 5.0 cm in a water-equivalent phantom ($20 \times 20 \times 20$ cm^3) (Fig. 1). Lipiodol, an ethiodised oil injection, is a sterile injectable radio-opaque diagnostic agent. On the MC calculation, the cross-section data and physical density were assigned. In our study, the cross-section data on PHITS that EGS was incorporated was used and the material data was used Lipiodol that was each millilitre contains 480 mg of iodine organically combined with the ethyl esters of fatty acids of poppy seed oil [29]. The physical density of Lipiodol was set to 1.28 g/cm^3. A 5×5 cm^2 field was used for irradiation at an SSD = 90 cm. The PDD was measured and normalized to the calculated dose at D_{max}.

2.2. SF and RBE calculation with MC

The SF and RBE were calculated using the PHITS code, and the phantom setup was the same as in the previous section. A mathematical function that expresses the microdosimetric probability densities (PDs) as a function of the charge, energy, and LET of ionising particles is incorporated in the PHITS code to calculate the PDs in macroscopic matter within a reasonable computational time. It is owing to this that it cannot be applied to the track-structure simulation, as it employs the local deposition approximation for ionising energy around the trajectory of the charged particle so as to reduce computational time for macroscopic particle transport simulation. Microdosimetric quantities, such as y, are generally regarded as better indices for expressing the RBE of photon beams, as they are directly related to the ionising densities in microscopic sites. The microdosimetric PDs at the target locations of the cell-survival fraction measurements can generally not be calculated by simulation codes [30], as those experiments are usually carried out with decelerated beams that consist of not only the primary particles, but also varieties of secondary particles produced in energy degraders. Therefore, the macroscopic calculation of fluences and energy spectra as well as the microscopic track-structure simulation